REMARKS

Applicant intends this response to be a complete response to the Examiner's **17 January 2006** Final Office Action. Applicant has labeled the paragraphs in his response to correspond to the paragraph labeling in the Office Action for the convenience of the Examiner.

Claim Rejections - 35 USC § 102/103

4. **Claims 7-8, 10, 12-13, 15, 21-29, 31, 35-40 and 42-47** stand rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kao et al. (6,399,335 B1).

The Examiner contends as follows:

> Kao et at. provides methods and compositions for polymerizing a particular nucleotide with a polymerase. In general, the method involves (a) forming a mixture of a polymerase and a nucleoside triphosphate (NTP) comprising α, β and γ phosphates and a γ-phosphate phosphoester-linked functional group; and (b) incubating the mixture under conditions wherein the polymerase catalyzes cleavage of the NTP between the α and β phosphates, liberating a pyrophosphate comprising the functional group and polymerizing the resultant nucleoside monophosphate. *i.e.* incorporates the nucleoside monophosphate in a nascent polynucleotide. Col. 2-4.
>
> A variety of functional groups compatible with the polymerization reaction are provided. In one embodiment, the functional group is a detectable label and the method further comprises the step of detecting the label, wherein a wide variety of chromogenic and luminogenic labels are provided.
>
> In another embodiment, the functional group is a cell delivery enhancing moiety, – OR, wherein R is independently selected from: substituted or unsubstituted (C1-C18) alkyl, alkenyl, alkynyl and aryl, each inclusive of carbocyclic and heterocyclic. These substituents provide enhanced therapeutic availability through enhanced gut or blood stability, cellular and/or membrane permeability, host phosphatase stability, *etc.* This aspect provides a wide variety of generally membrane permeable, relatively hydrophobic R substituents.
>
> The invention provides kits for assaying polymerase reactions in standard laboratory spectrophotometers. The kits are designed so that the researcher can replace one or more components with the sample they wish to test.
>
> Col. 4 shows exemplary of detectable label (Table 1A (4aminophenol for example) and labeled NTP's (Table 1 B). see also col. 7-12 . Which are viewed to be inclusive of the instant claims 23-26 for example.

Applicants claims are directed to a method for using modified nucleotides to alter (specifically, increase) incorporation fidelity using tagged dNTPs or tagged ddNTPs. Although Kao et al discloses sequencing reactions using tagged dNTPs, neither Kao et al nor any other reference disclose that tagged or labeled nucleotides would increase polymerase incorporation

fidelity. The discovery of the ability for tagged dNTPs to alter polymerase fidelity is novel and non-obvious as it permits artisans to improve sequencing and nucleotide library construction using enzymes that would not generally be suitable for such uses due to their frequency of mis-incorporations. Kao et al do not disclose the use the tagged dNTPs to increase polymerase fidelity. No one of ordinary skill would understand Kao et al to disclose or even suggest such an outcome. The use of tagged nucleotides to construct methods where unsuitable polymerases can be made suitable, or to construct libraries of nucleotides with varying amounts of fidelity - tuned, random mis-incorporations - is made possible only by this invention. Yet, nothing in Kao et al discloses or suggests such methods.

Because Kao et al do not disclose **the use of modified nucleotides to alter polymerase incorporation fidelity**, Kao et al cannot anticipate this invention. While clearly Kao et al disclose a method for polymerizing nucleotides – especially tagged nucleotide, Kao et al is silent as to the use of such nucleotide to alter, especially to increase, polymerase incorporation fidelity. Applicants, therefore, respectively request withdrawal of this rejection.

5. **Claims 7, 8, 10-13, 15, 21-24, 27-29, 31-33,36-40, 42-44, and 47** stand rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Williams (WO 00/36151).

The Examiner contends as follows:

> Williams et al. provide assay methods for the detection of pyrophosphate cleavage, which is advantageous in number of biological reactions. For example, in DNA polymerase reaction (pages 7-8). William et al. discloses a method comprising the step of adding a modified nucleotide having a y-phosphate with a fluorophore moiety attached thereto (pages 4-5, 16). Said method comprising a nucleotide polymerizing agent (polymerase). Further page 19 discloses that there are many linking moieties and methodologies for attaching fluorophore to nucleotides. Figure 4 shows the preferred linkers, which is viewed to be inclusive of instant claim 24. Additionally page 21 shows that the linker can comprised aryl groups (line 13). Suitable fluorophore include EDANS, (page 17, last paragraph). Page 7 shows that suitable NTPs include ATP. Williams et al. provides kits and integrated for practicing the assays (page 5). The polymerase is a DNA polymerase such as DNA polymerase I, II, or Ill, for example (page 8).

Like Kao et al, Williams et al cannot be used to suggest altering fidelity and the vast benefits altering polymerase fidelity can afford artisans involved in nucleotide sequencing or in nucleotide

library construction. Using tagged dNTPs to change mis-incorporation at will – simply by including or excluding tagged dNTPs – is not suggested by Williams et al.

Because Williams et al does not suggest **the use of modified nucleotides to alter incorporation fidelity**, Williams et al cannot anticipate this invention. Applicants, therefore, respectively request withdrawal of this rejection.

The Commissioner is authorized to charge the additional claim charges to Deposit Account No. 501518. The Commissioner is also authorized to charge any underpayment or credit any overpayment to Deposit Account No. 501518.

If you have any questions, please call me at 713.977.7000.

Respectfully Submitted,

Date: **May 22, 2006**

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